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Docket No.: PF-0041-4 CON

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1647

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Coleman et al.

Title: POLYNUCLEOTIDES ENCODING THROMBIN RECEPTOR HOMOLOGS

Serial No.:	09/997,522	Filing Date:	November 28, 2001
Examiner:	Landsman, R.S.	Group Art Unit:	1647

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BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed May 7, 2003, and received at the Patent Office on May 12, 2003, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the $320 fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 3-7, 9, 10, 12, 13, 57, and 58 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Corporation), (Reel 7660, Frame 0958) which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 3-7, 9, 10, 12, 13, 57, and 58
Claims allowed:	none
Claims canceled:	Claims 2, 8, 11, 17-27, 30-45, and 48-55
Claims withdrawn:	Claims 1, 14-16, 28, 29, 46, 47, and 56
Claims on Appeal:	Claims 3-7, 9, 10, 12, 13, 57, and 58 (A copy of the claims on appeal, as amended, can be found in the attached Appendix.)

(4) STATUS OF AMENDMENTS AFTER FINAL

No amendments were submitted after Final Rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to polynucleotides, comprising the polynucleotide sequence of SEQ ID NO:1, encoding G-protein coupled seven transmembrane receptor TRH, comprising the amino acid sequence of SEQ ID NO:2 (Specification, e.g., at page 1, lines 15-18; page 4, lines 27-29; page 5, lines 16-19; page 7, lines 25-28; and Figures 1A and 1B). Appellants' invention includes polynucleotides encoding a naturally occurring amino acid sequence wherein the naturally occurring amino acid sequence differs from SEQ ID NO:2 by a substitution of one amino acid residue (e.g., at page 6, lines 5-8) and/or an insertion of 1-5 amino acid residues (e.g., at page 6, lines 8-9) and/or a deletion of 1-5 amino acid residues (e.g., at page 6, lines 8-9). The invention also includes polynucleotides encoding a thrombin-binding fragment of SEQ ID NO:2 (e.g., at page 6, lines 12-17), polynucleotides encoding immunogenic fragments comprising at least 13 contiguous amino acid residues

of SEQ ID NO:2 (e.g., at page 6, lines 12-17), polynucleotides which are naturally occurring human variants of SEQ ID NO:1 (e.g., at page 5, lines 22-25; and page 7, lines 10-23), polynucleotides comprising at least 60 contiguous nucleotides of SEQ ID NO:1 (e.g., at page 6, lines 12-13; and page 6, line 23 to page 7, line 16), recombinant polynucleotides comprising polynucleotides of SEQ ID NO:1 (e.g., at page 8, line 30 to page 9, line 6), host cells comprising polynucleotides of SEQ ID NO:1 (e.g., at page 11, lines 15-23), and methods of making polypeptides encoded by polynucleotides of SEQ ID NO:2 (e.g., at page 11, lines 12-32).

TRH, encoded by polynucleotides of the invention, is 381 amino acid residues in length (e.g., Figures 1A, 1B, 2A, 2B, and 2C), and has strong chemical and structural homology to G-protein coupled transmembrane receptors (e.g., at page 1, lines 15-18). In particular, TRH is homologous to but significantly different from the GenBank sequence, HUMTHRR (e.g., at page 7, lines 27-28; and Figures 2A, 2B, and 2C). The GenBank sequence HUMTHRR is the sequence of the human thrombin receptor, which is a G-protein coupled transmembrane receptor (e.g., at page 2, lines 23-24). Furthermore, TRH displays amino acid sequence similarity to amino acid residues 94-155 of platelet activating factor receptor, which are amino acid residues covering most of transmembrane segment (TMS) III, the second intracellular loop, and TMS IV (e.g., page 2, lines 10-13 and 24-26; and Figures 2A, 2B, and 2C). Polynucleotides encoding TRH were first isolated from "the cDNAs of a liver library" (e.g., at page 7, lines 25-26), and can be "useful in investigations of and interventions in the normal and abnormal physiologic and pathologic processes which regulate cell signalling, immunity, repair, etc." (e.g., at page 7, lines 28-31).

The polynucleotides of the present invention are useful, for example, for toxicology testing, drug discovery, and disease diagnosis (Specification, e.g., at page 7, lines 3-9; and page 10, lines 20-28).

(6) ISSUES

1. Whether claims 3-7, 9, 10, 12, 13, 57, and 58 meet the utility requirement of 35 U.S.C. § 101.

2. Whether claims 3-7, 9, 10, 12, 13, 57, and 58 meet the enablement requirement of 35 U.S.C. § 112, first paragraph, i.e., would the specification enable one of ordinary skill in the art to make and use the claimed polynucleotides, e.g., for toxicology testing, drug development, and the diagnosis of disease.

3. Whether claims 3-7, 9, 10, 12, 13, 57, and 58 meet the enablement requirement of 35 U.S.C. § 112, first paragraph, with respect to the claimed "variants" and "fragments."

4. Whether claims 3, 6, 7, 9, 12, 13, and 58 meet the written description requirement of 35 U.S.C. § 112, first paragraph.

5. Whether claims 4, 5, and 57 are unpatentable over claims 1 and 3 of prior U.S. Patent No. 5,686,597, based on alleged statutory double patenting under 35 U.S.C. § 101.

6. Whether claims 3, 4, 5, 12, 13, and 57 are unpatentable over claim 1 of U.S. Patent No. 5,869,633, based on alleged obviousness-type double patenting.

7. Whether claims 3, 4, 5, 12, 13, and 57 are unpatentable over claims 1 and 3 of U.S. Patent No. 5,686,597, based on alleged obviousness-type double patenting.

8. Whether claim 6 is unpatentable over claim 2 of U.S. Patent No. 5,686,597, based on alleged obviousness-type double patenting.

9. Whether claims 9 and 10 are unpatentable over claim 6 of U.S. Patent No. 5,686,597, based on alleged obviousness-type double patenting.

10. Whether claims 6 and 7 are unpatentable over claims 4 and 5 of U.S. Patent No. 5,686,597, based on alleged obviousness-type double patenting.

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

As to Issue 3

Claims 3, 6, 7, 9, 12, 13, and 58 are grouped together, and claims 4, 5, 10, and 57 are grouped together.

As to Issue 4

Claims 3, 6, 7, 9, 12, 13, and 58 are grouped together.

As to Issue 5

Claims 4, 5, and 57 are grouped together.

As to Issue 6

Claims 3, 4, 5, 12, 13, and 57 are grouped together

As to Issue 7

Claims 3, 4, 5, 12, 13, and 57 are grouped together

As to Issue 8

Claim 6 is grouped by itself.

As to Issue 9

Claims 9 and 10 are grouped together.

As to Issue 10

Claims 6 and 7 are grouped together.

(8) APPELLANTS' ARGUMENTS

Issue 1 – Whether the claims on appeal meet the utility requirement of 35 U.S.C. § 101

The rejection of claims 3-7, 9, 10, 12, 13, 57, and 58 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in human liver tissue (Specification, e.g., at page 4, lines 28-29; and page 7, lines 25-26). The claimed polynucleotide encodes a polypeptide demonstrated in the patent specification to be a member of the G-protein coupled seven transmembrane receptor (T7G) protein family (also known as the GPCR family), whose biological functions include transmitting signals across plasma membranes in reponse to specific stimuli. More specifically, the claimed polynucleotide encodes a homolog of a human thrombin receptor (e.g., at page 2, lines 21-24; page 4, lines 27-29; page 7, lines 25-28; and Figures 2A, 2B, and 2C), which is useful, for example, in triggering cell proliferation in response to vascular injury (e.g., at page 1, lines 26-31). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide encoded by the claimed polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

The fact that the polypeptide encoded by the claimed polynucleotides is a member of the T7G protein family alone demonstrates utility. Each of the members of this class, regardless of their particular functions, are useful. There is no evidence that any member of this class of polypeptides, let alone a substantial number of them, would not have some patentable utility. It follows that there is a more than substantial likelihood that the polypeptide encoded by the claimed polynucleotides also has patentable utility, regardless of its actual function. The law has never required a patentee to prove more.

There is, in addition, direct proof of the utility of the claimed invention. Appellants submit with this brief the declaration of Lars Michael Furness (of record; originally submitted on November 15, 2002) describing some of the practical uses of the claimed invention in gene and protein expression

monitoring applications as they would have been understood at the time of filing of the patent application. The Furness Declaration describes, in particular, how the polypeptide encoded by the claimed polynucleotides can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate. (Furness Declaration at ¶ 10).

The Examiner does not dispute that the polypeptide encoded by the claimed polynucleotides can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Examiner contends that the polypeptide cannot be useful without precise knowledge of its biological function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotides in the absence of any knowledge as to the precise function of the polypeptide encoded by the claimed polynucleotides. The uses of the polypeptide encoded by the claimed polynucleotides for gene and protein expression monitoring applications including toxicology testing are in fact independent of its precise biological functions.

The Examiner asserts that the asserted utility of the claimed polynucleotides in toxicology testing is not specific because "[a]ny protein can be used in these screening assays" (Office Action, February 12, 2003; page 3). In addition, the Examiner contends that "in the absence of any disclosed relationship between the claimed polypeptides and any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. It is the group of proteins *as a whole* which may have a utility in toxicology screening" (Office Action, February 12, 2003; page 3; emphasis in original). This is incorrect. While it is true that all polynucleotides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific, substantial, and credible. A toxicology test using any particular expressed polynucleotide is dependent on the **identity** of that polynucleotide, not on its biological

function or its disease association. The results obtained from using any particular human-expressed polynucleotide in toxicology testing is specific to both the compound being tested and the polynucleotide used in the test. No two human-expressed polynucleotides are interchangeable for toxicology testing because the effects on the expression of any two such polynucleotides will differ depending on the identity of the compound tested and the **identities** of the two polynucleotides. It is not necessary to know the biological functions and disease associations of the polynucleotides in order to carry out such toxicology tests. Therefore, a "disclosed relationship between the claimed polypeptides and any disease or disorder" is **not** required for the claimed polynucleotides to have a specific and substantial utility in toxicology testing. At the very least, the claimed polynucleotides are specific controls for toxicology tests in developing drugs targeted to other polynucleotides, and are clearly useful as such.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examining Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Examiner bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Examiner must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Examiner makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Production of a polypeptide which is useful in protein expression applications, including the techniques of two-dimensional polyacrylamide gel electrophoresis and western blot analysis, for drug development and toxicity testing, are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Furness Declaration accompanying this brief. Objective evidence, not considered by the Patent Examiner, further corroborates the credibility of the asserted utilities.

A. The membership of the polypeptide encoded by the claimed polynucleotides in the T7G protein family demonstrates utility

Because there is a substantial likelihood that the TRH polypeptide is a member of the family of polypeptides known as G-protein coupled seven transmembrane receptors (T7Gs), the members of which are indisputably useful, there is by implication a substantial likelihood that the polypeptide encoded by the claimed polynucleotides is similarly useful. Appellants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed that the polypeptide encoded by the claimed polynucleotides is a protein having the sequence shown as SEQ ID NO:2 in the patent application and referred to as TRH in that application. Appellants have demonstrated by more than reasonable probability that TRH is a member of the T7G family of proteins. For example, TRH "is homologous to but significantly different from the GenBank sequence, HUMTHRR" (e.g., at page 7, lines 27-28; and Figures 2A, 2B, and 2C). HUMTHRR is a human thrombin receptor, a T7G protein (e.g., at page 2, lines 23-24). In addition, TRH "displays amino acid sequence similarity to platelet activating factor receptor (residues 94-155). These amino acids cover most of TMS III, the second intracellular loop, and TMS IV" (e.g., at page 2, lines 24-26; and Figures 2A, 2B, and 2C). Furthermore, the Examiner has acknowledged that "the protein of the present invention would inherently encode a thrombin receptor" (Office Action, September 3, 2002; page 11, § 9A).

The Examiner must accept the Appellants' demonstration that the polypeptide encoded by the claimed polynucleotides is a member of the T7G protein family and that utility is proven by a reasonable probability unless it can be demonstrated through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility.

Nor has the Examiner provided any evidence that any member of the T7G protein family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the polypeptide encoded by the claimed polynucleotides must, like the other members of the T7G protein family, be useful.

While the Examiner has cited literature identifying some of the difficulties that may be involved in predicting protein function, none suggests that functional homology cannot be inferred by a reasonable probability in this case. Skolnick et al., Trends Biotechnol., 2000, 18:34-39; Bork, Genome Res., 2000, 10:398-400; Doerks et al., Trends Genet., 1998, 14:248-250; Smith et al., Nat. Biotechnol., 1997, 15:1222-1223; Brenner et al., Trends Genet., 1999, 15:132-133; Bork et al., Trends Genet., 1996, 12:425-427. Importantly, none contradicts Bork's findings in the Bork (2000) reference that there is a 70% accuracy rate for bioinformatics-based predictions in general, and a 90% accuracy rate for the prediction of functional features by homology. Bork (2000), *supra*. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

Furthermore, the Examiner has asserted that "[i]n the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which bind to and/or mediate activity of the said receptor is clearly to use it as the object of further research" (Office Action, September 3, 2002; page 5). T7G proteins as a class are well known as proteins which transmit signals across plasma membranes in response to specific stimuli. As Mr. Furness discloses in his Declaration, T7G proteins "are targets of many current drug treatments, including anti-depressants,

anti-histamines, blood pressure regulators, and opiates. . . Even those T7Gs for which the specific ligand is not yet known are recognized in the art as highly valuable targets for novel drug discovery" (Furness Declaration, page 11, ¶ 12(a)). Newly identified T7Gs are used intensively in the real world, even in cases where neither the specific ligand which binds to the T7G protein nor the precise biological function of the T7G protein are known. Newly identified T7Gs are used, for example, as toxicology controls for drug candidates targeted to other T7Gs. TRH is immediately useful for such a purpose, without any further experimentation or any knowledge of "substances which bind to and/or mediate activity of" TRH.

The TRH polypeptide is useful even if the so-called "therapeutic" function of TRH is not known. For example, in toxicology testing, it is important to determine that a drug candidate targeted to a particular T7G protein does not have any effect on the expression or activity of any other T7G protein, and that the drug candidate does not bind to any other T7G protein. The TRH polypeptide can be used as a toxicology control to screen drug candidates directed to other T7G proteins so as to determine if the drug candidates affect the expression or activity of TRH, or bind to TRH. Thus, the TRH polypeptide is a research tool used to study the drug candidates and the T7G proteins to which they are targeted. It is not necessary for the Appellants to disclose a particular drug candidate to be screened in this way, given that the use of polypeptides in expression profiling and proteome analysis was well known at the time the priority application was filed (Furness Declaration at, e.g., ¶¶ 10-13). A novel member of the class of DNA ligases identified in the Patent Office's Training Materials, for instance, would presumably be considered to possess utility absent a disclosure of the specific DNAs it would be used to ligate. The Patent Office must apply consistent standards to similar categories of inventions, such as T7G proteins.

B. The uses of the polypeptide encoded by the claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene and protein expression profiling. These uses are explained in detail in the accompanying Furness Declaration, the substance of which is not

rebutted by the Examiner. There is no dispute that the claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

The instant application is a continuation of, and claims priority to, Coleman et al. (U.S. Ser. No. 09/643,383, filed August 21, 2000, hereinafter "the Coleman '383 application"), which is a divisional of, and claims priority to, Coleman et al. (U.S. Ser. No. 09/217,101, filed December 21, 1998; hereinafter "the Coleman '101 application"), which is a divisional of, and claims priority to, Coleman et al. (U.S. Ser. No. 08/911,320, filed August 14, 1997; hereinafter "the Coleman '320 application"), which is a divisional of, and claims priority to, Coleman et al. (U.S. Ser. No. 08/467,125, filed June 6, 1995; hereinafter "the Coleman '125 application"). The instant application and the Coleman '383, Coleman '101, Coleman '320, and Coleman '125 applications were filed with essentially identical specifications, with the exception of corrected typographical errors and reformatting. Thus page and line numbers may not match as between the instant application and the Coleman '383, Coleman '101, Coleman '320, and Coleman '125 applications.

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Coleman '125 application on June 6, 1995 would have understood that application to disclose the polypeptide encoded by the claimed polynucleotides to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs (Furness Declaration at, e.g., ¶¶ 10-13). Much, but not all, of Mr. Furness' explanation concerns the use of the polypeptide encoded by the claimed polynucleotides in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. Furness Declaration at ¶ 10.

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states of tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Coleman '125 application . . . and other related pre- and post-June 1995 publications, persons skilled in the art on June 6, 1995 clearly would have understood the Coleman '125 application to disclose the SEQ ID NO:2 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and for monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity. . . (Furness Declaration, page 8, ¶ 10)

> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:2 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating immune disorders and trauma for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, page 10, ¶ 12)

Mr. Furness' observations are confirmed in the literature published before and after June 1995. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, form the basis of two-dimensional gel databases. (Wilkins at page 26, Furness Declaration at Tab C).

C. The use of polypeptides expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Mr. Furness in his declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: Practicalities, problems, and potential, Xenobiotica, 1999, 29:655-691:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rockett et al., page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis, 1999, 24:153-159; Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters, 2000, 112-113:467-471.

The more genes -- and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator of the Nuwaysir article, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic

information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the rejections should be overturned regardless of their merit.

D. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the sequences of the claimed polynucleotides and the encoded polypeptide, and millions of

other sequences, throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's invention of the polypeptide encoded by the claimed polynucleotides, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the polypeptide encoded by the claimed polynucleotides are not "credible, specific and substantial" utilities. (Office Action, February 12, 2003; page 3). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The precise biological role or function of an expressed polypeptide is not required to demonstrate utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the polypeptide encoded by the claimed polynucleotides, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the polypeptide encoded by the claimed polynucleotides by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is

not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, e.g., ¶¶ 10-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any polypeptide or polynucleotide invention, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a class of useful products can be proof of utility

Despite the uncontradicted evidence that the polypeptide encoded by the claimed polynucleotides is a member of the T7G protein family, whose members indisputably are useful, the Examiner refused to impute the utility of the members of this class to TRH. In the Office Action of February 12, 2003, the Examiner takes the position that unless Appellants can identify which particular

biological function within the class of T7G proteins is possessed by TRH, utility cannot be imputed (Office Action, February 12, 2003; page 2, § 3A). To demonstrate utility by membership in the class of T7G proteins, the Examiner would require that all T7G proteins possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. See *Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a substantial number of useless members. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. See, *e.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).[1]

The Examiner addresses TRH as if the general class in which it is included is not the class of T7G proteins, but rather all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the class of T7G proteins does not. The T7G protein family is sufficiently specific to rule out any reasonable possibility that TRH would not also be useful like the other members of the family.

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[1]At a recent Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

Because the Examiner has not presented any evidence that the T7G class of proteins has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that TRH is useful.

Even if the Examiner's "common utility" criterion were correct – and it is not – the class of T7G proteins would meet it. It is undisputed that known members of the class of T7G proteins transmit signals across plasma membranes in response to specific stimuli. A person of ordinary skill in the art need not know any more about how the polypeptide encoded by the claimed polynucleotides transmits signals across plasma membranes to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given T7G protein transmits signals in response to a given stimulus. The Examiner then goes on to assume that the only use for polynucleotides which encode TRH absent knowledge as to how this member of the T7G protein family actually works is further study of TRH itself.

Not so. As demonstrated by Appellants, knowledge that TRH is a T7G protein is more than sufficient to make the polypeptide encoded by the claimed polynucleotides useful for the diagnosis and treatment of immune disorders and trauma. Indeed, TRH has been shown to be expressed in liver tissue. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

C. The uses of TRH in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

The Examiner rejected the claims at issue on the ground that the use of an invention as a tool for research is not a "substantial" use. Because the Examiner's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (M.P.E.P. § 2107.01):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are

> useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the Patent Office's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Furness Declaration. The Furness Declaration demonstrates that the claimed invention is a tool, rather than an object, of research, and it demonstrates exactly how that tool is used. Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about the polypeptide encoded by the claimed polynucleotides.

The use of the claimed invention as a research tool in toxicology testing is specific and substantial. While it is true that all polypeptides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific and substantial. A toxicology test using any

particular expressed polypeptide is dependent on the **identity** of that polypeptide, not on its biological function or its disease association. The results obtained from using any particular human-expressed polypeptide in toxicology testing is specific to both the compound being tested and the polypeptide used in the test. **No two human-expressed polypeptides are interchangeable for toxicology testing** because the effects on the expression of any two such polypeptides will differ depending on the identity of the compound tested and the **identities** of the two polypeptides. It is not necessary to know the biological functions and disease associations of the polypeptides in order to carry out such toxicology tests. Therefore, at the very least, the polypeptide encoded by the claimed polynucleotides is a specific control for toxicology tests in developing drugs targeted to other polypeptides, and is clearly useful as such.

As an example, a histone protein expressed in humans can be used in a specific and substantial toxicology test in drug development. A histone protein may not be suitable as a target for drug development because disruption of such a protein may kill a patient. However, a human-expressed histone protein is surely an excellent subject for toxicology studies when developing drugs **targeted to other proteins**. A drug candidate which alters expression of a histone protein is toxic because disruption of such a pervasively-expressed protein would have undesirable side effects in a patient. Therefore, when testing the toxicology of a drug candidate targeted to another protein, measuring the expression of a histone protein is a good measure of the toxicity of that candidate, particularly in *in vitro* cellular assays at an early stage of drug development. The utility of any particular human-expressed histone protein in toxicology testing is specific and substantial because a toxicology test using that histone protein cannot be replaced by a toxicology test using a different protein, including any other histone protein. This specific and substantial utility requires no knowledge of the biological function or disease association of the histone protein.

The Examiner assails this logic by arguing that "it is clear what can happen to a patient with altered histone function since these protein have been thoroughly characterized. The function of the protein of the present invention is not clear since, unlike the exemplified histones, has not been characterized" (Office Action, February 12, 2003; page 4). The Examiner has ignored the fact that the utility described above does not depend on knowing either the biological function or disease association

of the exemplified histone. It is the fact that the example protein is expressed in human tissue that allows the protein to be used as a control when measuring the toxicity of a drug candidate targeted to another protein. Likewise, the polypeptide encoded by the claimed polynucleotides can be used as a control in toxicology testing without knowing anything about its biological function or disease association.

The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include diagnostic assays (Specification, e.g., at page 10, lines 20-28), chromosomal mapping (e.g., at page 10, line 29 to page 11, line 11), testing of chimeric T7G proteins (e.g., at page 19, line 30 to page 21, lines 2), competitive drug screening assays (e.g., at page 23, line 25 to page 24, line 25), and identification of signal transduction proteins (e.g., at page 25, line 22 to page 26, line 7).

D. The Patent Examiner failed to demonstrate that a person of ordinary skill in the art would reasonably doubt the utility of the claimed invention

Based principally on citations to scientific literature identifying some of the difficulties involved in predicting protein function, the Examiner rejected the pending claims on the ground that the Appellants cannot impute utility to the claimed invention based on the homology of the polypeptide encoded by the claimed polynucleotides to other polypeptides which are useful. The Examiner's rejection is both incorrect as a matter of fact and as a matter of procedural law.

As demonstrated in § II.A, *supra*, the literature cited by the Examiner is not inconsistent with the Appellants' proof of homology by a reasonable probability. It may show that Appellants cannot prove function by homology with **certainty**, but Appellants need not meet such a rigorous standard of proof. Under the applicable law, once the Appellants demonstrate a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. See *In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not made such a showing and, as such, the Examiner's rejection should be overturned.

In the present case, the Examiner has contended that the similarity of TRH to known T7G proteins is insufficient to establish that TRH is a member of the T7G protein family and thus shares the same utilities. The Examiner attempted to support this assertion with the teachings of Skolnick et al. (Trends Biotechnol., 2000, 18:34-39), Bork (Genome Res., 2000, 10:398-400), Doerks et al. (Trends Genet., 1998, 14:248-250), Smith et al. (Nat. Biotechnol., 1997, 15:1222-1223), Brenner et al. (Trends Genet., 1999, 15:132-133), and Bork et al. (Trends Genet., 1996, 12:425-427), all of record and addressed below. However, all of these references fail to support the outstanding rejections.

The Examiner cites the Skolnick reference as evidence that "knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36)" (Office Action, September 3, 2002; page 4). "Box 2" of the Skolnick reference speaks only to the fact that the three-dimensional structure of a protein does not always lead to the assignment of function with certainty. This portion of the Skolnick reference says nothing at all about assigning function based on **sequence homology**, as in the present case. In fact, the Skolnick reference recognizes that assigning function based on sequence homology is a "powerful" method (Skolnick et al., page 34, right-hand column, third paragraph). As such, the Skolnick reference supports the notion that TRH has the utilities and biological functions of T7G proteins.

The use of sequence comparisons to predict protein function is further supported by the Bork (2000) reference, cited by the Examiner. Bork (2000) discloses a 70% accuracy rate in bioinformatics-based predictions. This more than meets the legal standard of utility, which requires only that one of skill in the art would **more likely than not** believe the utility of the claimed invention. For predicting functional features by homology, Table 1 of Bork (2000) discloses a 90% accuracy rate, even greater than the 70% rate for all bioinformatics predictions.

The Examiner uses the teachings of the Doerks reference as evidence that "functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein," and that "overpredictions of functionality occur because structural similarity does not necessarily coincide with functional similarity" (Office Action, September 3, 2002; pages 4-5). Doerks et al. examined 1300 protein sequences that were in

"uncharacterized protein families" (Doerks et al., page 248, column 1, paragraph 2; and page 250, column 1, paragraph 2). These sequences comprise a sample set chosen specifically because of difficulties in functional annotation. Thus, this reference is not relevant to the **general validity** of using sequence homology to assign protein function. In fact, as discussed above, Bork (one of the coauthors of the Doerks reference) has shown that there is a 70% accuracy rate for bioinformatics-based predictions in general, and a 90% accuracy rate for the prediction of functional features by homology.

The Examiner cites the Smith reference to support the assertion that "there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene" (Office Action, September 3, 2002; page 5). However, the fact that there may be a number of examples in which the assignment of function by sequence homology is not perfectly accurate does not contradict the findings of Bork (2000) that, **in general**, sequence homology is an accurate method for assigning biological function.

The Examiner cites the Brenner reference as further evidence that "accurate inference of function from homology must be a difficult problem" (Office Action, September 3, 2002; page 5). The difficulty of this problem is not relevant to the issue at hand. In spite of the "difficulty of this problem," Bork (2000) has shown that the prediction of functional features by homology has a 90% accuracy rate (Bork (2000), Table 1 on page 399). In fact, this 90% accuracy rate was determined in part from the data presented by Brenner et al. (see the citation of Brenner et al. in the fifth column of Table 1 of Bork (2000)). The legal standard for utility requires only that one of skill in the art would **more likely than not** believe the utility of the claimed invention. Therefore, the disclosure in Bork (2000) of a 90% accuracy rate for the prediction of functional features by homology shows that such methods are more than adequate for supporting a patentable utility.

In further support of the rejection, the Examiner cites the findings of Bork (1996) that "the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts" (Office Action, September 3, 2002; page 5). However, this reference does not negate the fact that there is a 90% accuracy rate for the prediction of functional features by homology,

as disclosed by Bork (2000). At most this reference shows that errors can occur in functional assignment. Bork (2000) does not show that errors do not occur; however, this later Bork reference quantifies the error rate at about 10%.

Furthermore, it is irrelevant that "software robots" sometimes make errors in assigning protein function because no such "software robots" were used in the present case. The TRH polypeptide was scientifically determined to be a homolog of the human thrombin receptor HUMTHRR by **human inventors**, not by software robots. In addition, the biological functions of HUMTHRR were experimentally known in the art at the time the Coleman '125 application was filed, as evidenced by the numerous articles and reviews cited on the first two pages of the Specification. No error-prone "software robots" were involved in assigning biological functions to HUMTHRR.

The references cited by the Examiner show that there may be difficulties and errors involved in predicting protein function by homology. However, these references do not contradict the fact that such methods are accurate more often than not. As such, one of skill in the art would **more likely than not** believe that TRH has the utilities of the family of T7G proteins.

The Examiner contends that "Applicants have only shown that the protein of the present invention is homologous to HUMTHRR, but is significantly different. Furthermore, the protein of the present invention is also shown to be homologous to PAF, but only over certain regions. Therefore, the fact that the protein of the present invention is homologous to 2 different proteins further demonstrates that the function of this protein is not known" (Office Action, February 12, 2003; page 2, § 3A). This is incorrect. The polypeptide encoded by the claimed polynucleotides has "sequence similarity to platelet activating factor **receptor** (residues 94-155)" (Specification at page 2, lines 24-25; emphasis added), not platelet activating factor (PAF) itself. Since platelet activating factor receptor is, like thrombin receptor, a member of the family of T7G proteins, the homology between TRH and platelet activating factor receptor is further evidence that TRH is a T7G protein.

Moreover, the "certain regions" over which the TRH polypeptide is homologous to platelet activating factor receptor "cover most of TMS III, the second intracellular loop, and TMS IV" (Specification at page 2, lines 25-26). As disclosed in the specification, TMS III and TMS IV are two of the seven transmembrane segments which are characteristics of the family of T7G proteins

(Specification, e.g., at page 2, lines 10-13). Therefore, the homology between TRH and certain regions of platelet activating factor receptor provides additional evidence that TRH is a T7G protein.

As the cited evidence is completely insufficient to support the rejections of the claims, the outstanding rejections must be overturned for this reason alone. The only relevant evidence of record shows that a person of ordinary skill in the art would not doubt that the polypeptide encoded by the claimed polynucleotides is in fact a member of the family of T7G proteins, which are known to have specific utility.

IV. By Requiring the Appellants to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at page 52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel

the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge

of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.B (*Montedison,* 664 F.2d at 374-375).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. See *supra* § III.B. Thus the Training Materials cannot be applied consistently with the law.

Issue 2 – Whether the claims meet the enablement requirement of 35 U.S.C. § 112, first paragraph, with respect to the "utility" issue

To the extent the rejection of claims 3-7, 9, 10, 12, 13, 57, and 58 under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth by the Examiner is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Issue 3 – Whether claims 3-7, 9, 10, 12, 13, 57, and 58 meet the enablement requirement of 35 U.S.C. § 112, first paragraph, with respect to "variants" and "fragments"

Claims 3-7, 9, 10, 12, 13, 57, and 58 stand rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use the claimed variants and fragments. In particular, the Examiner asserts that "[a]lthough the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention

as a starting point for further experimentation" (Office Action, February 12, 2003; page 5). Such, however, is not the case.

With respect to this rejection, claims 4, 5, 10, and 57 are separately patentable from claims 3, 6, 7, 9, 12, 13, and 58, because claims 4, 5, 10, and 57 are directed to inventions defined by SEQ ID NO:1 and/or SEQ ID NO:2. Claim 4 is drawn to polynucleotides encoding polypeptides comprising SEQ ID NO:2, claims 5 and 57 are drawn to polynucleotides comprising SEQ ID NO:1, and claim 10 is drawn to a method for producing a polypeptide comprising the sequence of SEQ ID NO:2. The Examiner's rejection is based on the alleged lack of enablement of polynucleotide and polypeptide **variants** and **fragments**, and thus should not apply to claims 4, 5, 10, and 57. For at least this reason, this rejection of claims 4, 5, 10, and 57 should be overturned.

With respect to this rejection, claims 3, 6, 7, 9, 12, 13, and 58 are separately patentable from claims 4, 5, 10, and 57, because claims 3, 6, 7, 9, 12, 13, and 58 are directed to inventions which include polynucleotide variants and fragments that one of skill in the art would know how to make and use, based on the Specification and the state of the art at the time the application was filed. For at least this reason, this rejection of claims 3, 6, 7, 9, 12, 13, and 58 should be overturned.

With respect to the claimed variants, the Examiner asserts that "Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions" (Office Action, February 12, 2003; page 5). Note that claim 3, for example, recites not only that the polynucleotides encode polypeptides which are variants of SEQ ID NO:2, but also that they have "**a naturally occurring amino acid sequence**." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:2 (the amino acid sequence of TRH) and SEQ ID NO:1 (the polynucleotide sequence encoding TRH), one of skill in the art would be able to routinely obtain "a naturally occurring amino acid sequence" which was a variant of SEQ ID NO:2.

For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, e.g., page 9, lines 7-20. Thus, one skilled in the art need not make and test vast numbers of polynucleotides that encode polypeptides based on the amino acid sequence of SEQ ID NO:2, or vast numbers of polynucleotides based on the polynucleotide sequence of SEQ ID NO:1. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides, and their encoded polypeptides, that already exist in nature. By adjusting the nature of the probes or nucleic acids (i.e., non-conserved, conserved, or highly conserved) and the conditions of hybridization (maximum, high, intermediate, or low stringency), one can obtain variant polynucleotides of SEQ ID NO:1 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:2 recited by the present claims using conventional techniques of recombinant protein production. By extension, one of skill in art could make fragments of naturally occurring human variants of the SEQ ID NO:1 polynucleotide, and could use such fragments, for example, as hybridization probes to detect full-length human variants of the SEQ ID NO:1 polynucleotide. Similarly, a skilled artisan could make polynucleotides encoding fragments of the SEQ ID NO:2 polypeptide, and could use such fragments, for example, as hybridization probes to detect polynucleotides encoding full-length human variants of the SEQ ID NO:2 polypeptide.

The Examiner asserts that "variants often encode proteins with quantitatively or qualitatively altered or absent biological activity. Therefore, the specification does not teach how to use such variants, nor is adequate guidance provided for the skilled artisan to predict, *a priori*, which variants would reasonably be expected to retain biological function" (Office Action, February 12, 2003; page 5). This is incorrect. One of skill in the art would reasonably conclude that the claimed polynucleotides encode polypeptide variants having the functions of the polypeptide of SEQ ID NO:2. For example, Brenner et al. (Proc. Natl. Acad. Sci. USA, 1998, 95:6073-6078) teach that sequence homology as low as 30% over 150 amino acid residues, and as low as 40% over 70 amino acid residues, is indicative of protein homology. Furthermore, Bork (Genome Res., 2000, 10:398-400), cited by the Examiner, teaches that the prediction of functional features by homology has a 90% accuracy rate, and

that the accuracy rate for all bioinformatics predictions is 70% (Table 1 of Bork). Thus, one of skill in the art would reasonably understand that a polypeptide comprising a sequence which "differs from the amino acid sequence of SEQ ID NO:2 by a substitution of one amino acid residue and/or an insertion of 1-5 amino acid residues and/or a deletion of 1-5 amino acid residues" could be used in the same way as the polypeptide of SEQ ID NO:2.

Furthermore, it is irrelevant whether any of the claimed polynucleotides encode polypeptide variants which have "altered or absent biological activity." One of skill in the art would still know how to make and use such polynucleotides, without undue experimentation. For example, polynucleotides which encode nonfunctional polypeptide variants of SEQ ID NO:2 could be used to detect polynucleotides which encode the polypeptide of SEQ ID NO:2 by, for example, hybridization and/or PCR techniques. It is not necessary for a polynucleotide to encode a functional polypeptide for one of skill in the art to be able to use that polynucleotide without undue experimentation.

In addition, the Examiner has ignored the fact that the recited polynucleotide variants have specific, substantial, and credible utilities in, for example, toxicology testing in drug discovery (discussed above under Issue 1). One of skill in the art would know that, as a part of such toxicology testing, the recited polynucleotide variants could be used to detect toxic side effects of drug candidates targeted to other polynucleotides. Therefore, the claimed polynucleotides meet the enablement requirement of 35 U.S.C. § 112, first paragraph, based at least on the well-known, specific, and substantial utilities of expressed, naturally occurring, polynucleotides in toxicology testing.

The Examiner contends that "Applicants have amended the claims to recite that the 'naturally occurring amino acid sequence' differs from SEQ ID NO:2 by the substitution, insertion, or deletion of 1-5 residues. However, it is not known if the total number of alterations is at most 5, or if 1-5 alterations can occur at each amino acid residue of SEQ ID NO:2" (Office Action, February 12, 2003; page 4, § 4B). This contention ignores the wording of the claims. For example, claim 3 recites in part a polypeptide comprising a naturally occurring amino acid sequence wherein the sequence "differs from the amino acid sequence of SEQ ID NO:2 by a substitution of one amino acid residue and/or an insertion of 1-5 amino acid residues and/or a deletion of 1-5 amino acid residues." Thus, one of the possible differences between the recited naturally occurring amino acid sequence and SEQ ID NO:2 is

"**a** substitution of **one** amino acid residue." Therefore, the Examiner's assertion that the recited naturally occurring amino acid sequence differs from SEQ ID NO:2 by "the **substitution**, insertion, or deletion **of 1-5 residues**" is incorrect. Other possible differences between the recited naturally occurring amino acid sequence and SEQ ID NO:2 include "**an** insertion of 1-5 amino acid residues" and "**a** deletion of 1-5 amino acid residues." A skilled artisan would understand how to obtain a naturally occurring amino acid sequence which differs from SEQ ID NO:2 by "a substitution of one amino acid residue and/or an insertion of 1-5 amino acid residues and/or a deletion of 1-5 amino acid residues" without undue experimentation. Therefore, the claimed polynucleotides which encode the recited polypeptide variants meet the enablement requirement of 35 U.S.C. § 112, first paragraph.

With respect to the claimed polynucleotides encoding thrombin-binding fragments of SEQ ID NO:2, the Examiner asserts that "the guidance provided by the specification would not be sufficient to enable the artisan to make the claimed fragment of SEQ ID NO:2 which binds thrombin. The protein of SEQ ID NO:2 is 381 residues in length and Applicants have not provided the artisan with any information (i.e., guidance or working examples) as to which residues are required to bind thrombin" (Office Action, February 12, 2003; page 5). The Specification discloses methods of measuring the binding of the SEQ ID NO:2 polypeptide, or a fragment thereof, to any "agent which can affect signal transduction," including thrombin (e.g., at page 23, line 26 to page 24, line 21). Therefore, one of skill in the art could make and use the claimed polynucleotides, without undue experimentation, based on the Specification and the state of the art at the time the application was filed. A skilled artisan could routinely make the claimed polynucleotides encoding thrombin-binding fragments of SEQ ID NO:2 by, for example, screening polypeptide fragments of SEQ ID NO:2 for thrombin-binding activity. The claimed polynucleotides encoding thrombin-binding fragments of SEQ ID NO:2 could be used, for example, to produce polypeptides for binding to and/or purifying thrombin. There is no need to predict "which residues would need to remain as part of the fragment in order to retain the thrombin-binding property of the fragment" (Office Action, February 12, 2003; page 5) because the claimed polynucleotides could be obtained by routine methods known in the art.

The Examiner states that "regarding *Marzocchi*, the Office believes that . . . the guidance provided by the specification would not be sufficient to enable the artisan to make the claimed fragment of SEQ ID NO:2 which binds thrombin" (Office Action, February 12, 2003; page 5). However, the "belief" that the guidance is insufficient does not adequately support an enablement rejection under 35 U.S.C. § 112, first paragraph. Evidence or sound scientific reasoning must be provided to support a rejection for lack of enablement.

With respect to the claimed fragments, the Examiner asserts that "[s]ince the utility of the nucleic acid molecule encoding SEQ ID NO:2 is not known, then the utility of any polynucleotide fragment thereof would also not possess utility" (Office Action, February 12, 2003; page 6). This is incorrect. One of skill in the art could make and use the claimed polynucleotide fragments, and the claimed polynucleotides encoding polypeptide fragments, without undue experimentation, based on the Specification and the state of the art at the time the application was filed. For example, one of skill in the art would know how to use the claimed polynucleotide fragments, and the claimed polynucleotides encoding polypeptide fragments, as hybridization probes or PCR probes to detect the presence of a polynucleotide comprising SEQ ID NO:2 (Specification, e.g., at page 6, lines 21-30; page 7, lines 3-16; page 8, lines 3-8; page 9, lines 7-20; and page 10, line 15 to page 11, line 11). Furthermore, as discussed above under Issue 1, polynucleotides encoding the SEQ ID NO:2 polypeptide do have specific, substantial, and credible utilities. For example, one of skill in the art would know that such polynucleotides could be used to detect toxic side effects of drug candidates targeted to other polynucleotides. Therefore, the claimed polynucleotide fragments could be used in toxicology testing for drug discovery.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited polynucleotides encoding polypeptide variants and fragments of SEQ ID NO:2, or the recited polynucleotide variants and fragments of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited variants and fragments of SEQ ID NO:1 and SEQ ID NO:2.

For at least the above reasons, reversal of this rejection is requested.

Issue 4 – Whether claims 3, 6, 7, 9, 12, 13, and 58 meet the written description requirement of 35 U.S.C. § 112, first paragraph

Claims 3, 6, 7, 9, 12, 13, and 58 stand rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter in such a way as to reasonably convey to one of skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner asserts that "only an isolated DNA molecule comprising a DNA sequence consisting of SEQ ID NO:1 and 2 and equivalent degenerative codon sequences thereof, as well as SEQ ID NO:2, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph" (Office Action, February 12, 2003; page 7). This rejection is traversed.

The Examiner states that "Applicants have not demonstrated that they were in possession of allelic variants of SEQ ID NO:1 or 2 at the time of the present invention. The concept of a naturally occurring allelic variant of SEQ ID NO:1 or 2 was, respectfully, merely an idea" (Office Action, February 12, 2003; page 7). By this statement, it appears that the Examiner would require an actual

reduction to practice of the claimed invention in order to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. However, an actual reduction to practice is not necessary.

There is no statutory requirement that an invention actually be reduced to practice in order for that invention to be patentable. The amino acid sequence of SEQ ID NO:2 and the polynucleotide sequence of SEQ ID NO:1 have been explicitly disclosed in the specification (see, e.g., the Sequence Listing). The concept of "naturally occurring variants" was well known in the art at the time the application was filed. Furthermore, variants of SEQ ID NO:1 and SEQ ID NO:2 are described in the specification at, for example, page 4, lines 30-32; page 5, lines 22-25; page 5, line 30 to page 6, line 11; page 7, lines 17-23; and page 8, lines 14-29. In conjunction with the disclosure in the specification and the knowledge in the art at the time the application was filed, a skilled artisan would reasonably conclude that Appellants were in possession of the claimed polynucleotide variants, and the claimed polynucleotides encoding the recited polypeptide variants, at the time the application was filed. Thus, the constructive reduction to practice of the claimed polynucleotides provides a more than adequate written description for the claimed invention.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*
> *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art

> need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. [footnotes omitted]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the claimed "variants" and "fragments" of SEQ ID NO:1 and SEQ ID NO:2.

The subject matter encompassed by claims 3, 6, 7, 9, 12, 13, and 58 is either disclosed by the specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 3 recites a polynucleotide encoding a polypeptide "comprising a naturally occurring amino acid sequence, wherein the naturally occurring amino acid sequence differs from the amino acid sequence of SEQ ID NO:2 by a substitution of one amino acid residue and/or an insertion of 1-5 amino acid residues and/or a deletion of 1-5 amino acid residues." Similarly, the "variant" language of independent claim 12 recites "a polynucleotide comprising a naturally occurring human variant of the polynucleotide sequence of SEQ ID NO:1." The amino acid sequence of SEQ ID NO:2 and the polynucleotide sequence of SEQ ID NO:1 are explicitly disclosed in the specification. See, for example, the Sequence Listing. Variants of SEQ ID NO:1 and SEQ ID NO:2 are described in the specification at, for example, page 4, lines 30-32; page 5, lines 22-25; page 5, line 30 to page 6, line 11; page 7, lines 17-23; and page 8, lines 14-29.

For example, the specification discloses that "as a result of the degeneracy of the genetic code, a multitude of TRH-encoding nucleotide sequences, some bearing minimal homology to the nucleotide sequence of any known and naturally occurring gene may be produced" (Specification, page 8, lines 14-16). One of ordinary skill in the art would recognize polynucleotide sequences which are TRH-encoding variants of SEQ ID NO:1, having codons which vary from those of SEQ ID NO:1. Given any naturally occurring polynucleotide sequence from humans, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:1. By extension, a skilled artisan would

recognize any polynucleotide comprising at least 60 contiguous nucleotides of such a variant of SEQ ID NO:1. Accordingly, the specification provides an adequate written description of the recited polynucleotide variants of SEQ ID NO:1 and the recited polynucleotides comprising at least 60 contiguous nucleotides of such variants.

Likewise, one of ordinary skill in the art would recognize polynucleotide sequences which encode polypeptide variants which differ from SEQ ID NO:2 by "a substitution of one amino acid residue and/or an insertion of 1-5 amino acid residues and/or a deletion of 1-5 amino acid residues." The Examiner contends that "Applicants have amended the claims to recite that the 'naturally occurring amino acid sequence' differs from SEQ ID NO:2 by the substitution, insertion, or deletion of 1-5 residues. However, it is not known if the total number of alterations is at most 5, or if 1-5 alterations can occur at each amino acid residue of SEQ ID NO:2" (Office Action, February 12, 2003; page 4, § 4B). This contention ignores the wording of the claims. For example, claim 3 recites in part a polypeptide comprising a naturally occurring amino acid sequence wherein the sequence "differs from the amino acid sequence of SEQ ID NO:2 by a substitution of one amino acid residue and/or an insertion of 1-5 amino acid residues and/or a deletion of 1-5 amino acid residues." Thus, one of the possible differences between the recited naturally occurring amino acid sequence and SEQ ID NO:2 is "**a** substitution of **one** amino acid residue." Therefore, the Examiner's assertion that the recited naturally occurring amino acid sequence differs from SEQ ID NO:2 by "the **substitution**, insertion, or deletion **of 1-5 residues**" is incorrect. Other possible differences between the recited naturally occurring amino acid sequence and SEQ ID NO:2 include "**an** insertion of 1-5 amino acid residues" and "**a** deletion of 1-5 amino acid residues." A skilled artisan would reasonably conclude that Appellants were in possession of naturally occurring amino acid sequences which differ from SEQ ID NO:2 by "a substitution of one amino acid residue and/or an insertion of 1-5 amino acid residues and/or a deletion of 1-5 amino acid residues." Therefore, given any naturally occurring polypeptide sequence, it would be routine for one of skill in the art to recognize whether it was one of the recited variants of SEQ ID NO:2. Accordingly, the specification provides an adequate written description of the recited polynucleotides encoding polypeptide variants of SEQ ID NO:2.

The "fragment" language of independent claim 3 recites polynucleotides encoding thrombin-binding fragments of the polypeptide of SEQ ID NO:2 or encoding immunogenic fragments comprising at least 13 contiguous amino acid residues of SEQ ID NO:2. Similarly, the "fragment" language of independent claim 13 recites polynucleotides comprising at least 60 contiguous nucleotides of SEQ ID NO:1 or a naturally occurring human variant of SEQ ID NO:1. Fragments of SEQ ID NO:1 and SEQ ID NO:2 are described in the specification at, for example, page 5, lines 16-17; page 6, lines 12-17 and 21-30; page 7, lines 3-9; page 9, lines 11-15; page 10, lines 15-19; page 12, lines 1-15; and page 21, lines 12-23. Methods of measuring the binding of the SEQ ID NO:2 polypeptide, or a fragment thereof, to any "agent which can affect signal transduction," including thrombin, are disclosed in the specification at, for example, page 23, line 26 to page 24, line 21. Methods to determine the immunogenicity of polypeptide fragments by measuring the specific binding of antibodies are disclosed in the Specification at, for example, page 12, lines 9-26; page 22, lines 7-11; and page 22, line 31 to page 23, line 2.

One of ordinary skill in the art would recognize polynucleotide sequences which are fragments of SEQ ID NO:1, which encode polypeptide sequences which are fragments of SEQ ID NO:2, or which encode polypeptide sequences which are fragments comprising at least 13 contiguous amino acid residues of SEQ ID NO:2. The information provided by SEQ ID NO:1 and SEQ ID NO:2 provides the necessary framework for the recited fragments -- to recite every possible fragment would needlessly clutter the application. Furthermore, it would be routine for one of skill in the art to determine whether any particular fragment of SEQ ID NO:2 possessed thrombin-binding activity, based on the disclosure in the specification and the state of the art at the time the application was filed. Likewise, it would be routine for one of skill in the art to determine whether any particular fragment of SEQ ID NO:2 had immunogenic activity, using methods disclosed in the specification and/or known in the art. Accordingly, the specification provides an adequate written description of the recited polynucleotide fragments of SEQ ID NO:1 and polynucleotides encoding the recited fragments of SEQ ID NO:2.

The Examiner asserts that the specification only defines "the term 'fragment' and briefly discuss 'immunogenic fragments' of SEQ ID NO:2. They do not provide any description of the sequence of

any 'thrombin-binding fragments.' . . . Applicants have not described which residues are critical to maintain the thrombin-binding characteristics of the claimed fragment" (Office Action, February 12, 2003; page 6). However, it is not necessary to describe the residues which are critical for maintaining the thrombin-binding activity of the SEQ ID NO:2 polypeptide in order to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. All that is required is that the specification reasonably convey to one of ordinary skill in the art that the Appellants were in possession of the claimed invention at the time the application was filed. Based on the disclosure in the specification and the state of the art at the time the application was filed, a skilled artisan would have reasonably concluded that Appellants were in possession of polynucleotides encoding the recited polypeptide fragments. For example, the explicit disclosure of the sequence of SEQ ID NO:2, and methods to determine thrombin-binding activity of any possible fragment of SEQ ID NO:2, satisfies the written description requirement for the claimed polynucleotides encoding the recited thrombin-binding fragments of SEQ ID NO:2.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written

> description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than functional characteristics. For example, the language of independent claims 3 and 9 recites chemical structure to define the claimed genus:

> 3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:
> a) a polypeptide comprising the amino acid sequence of SEQ ID NO:2,
> b) a polypeptide comprising a naturally occurring amino acid sequence, wherein the naturally occurring amino acid sequence differs from the amino acid sequence of SEQ ID NO:2 by a substitution of one amino acid residue and/or an

insertion of 1-5 amino acid residues and/or a deletion of 1-5 amino acid residues,

c) a thrombin-binding fragment of a polypeptide, wherein the polypeptide has the amino acid sequence of SEQ ID NO:2, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:2, wherein said fragment comprises at least 13 contiguous amino acid residues of SEQ ID NO:2.

12. An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:1,

b) a polynucleotide comprising a naturally occuring human variant of the polynucleotide sequence of SEQ ID NO:1,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides and polypeptides. The polynucleotides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base the written description inquiry "on whatever is now claimed," the Examiner failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

The Patent Office Guidelines indicate that evidence that Appellants were in possession of the claimed invention can include "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, **or** some combination of such characteristics" (P.T.O. Guidelines, *supra*; emphasis added). The claimed polynucleotides have been described by chemical structure (e.g., relation of the recited polynucleotides to SEQ ID NO:1, relation of the recited polypeptides to SEQ ID NO:2), physical properties (e.g., occurrence in nature of the recited variant sequences), and chemical properties (e.g.,

immunogenic activity or thrombin-binding activity of the recited polypeptide fragments). Therefore, the written description requirement has been met.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that, rather than being a large variable genus, the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA, 1998, 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to polynucleotides encoding G-protein coupled seven transmembrane receptor proteins (T7Gs), including polynucleotides encoding thrombin receptor homologs related to the amino acid sequence of SEQ ID NO:2. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as thrombin receptor homologs and which have as little as 30% identity over at least 150 residues to SEQ ID NO:2. The "variant language" of the present claims recites a polynucleotide encoding a polypeptide comprising "a naturally occurring amino acid sequence, wherein the naturally occurring amino acid sequence differs from the amino acid sequence of SEQ ID NO:2 by a substitution of one amino acid residue and/or an insertion of 1-5 amino acid residues and/or a deletion of 1-5 amino acid residues" (note that SEQ ID NO:2 has 381 amino acid residues). This variation is far less than that of polynucleotides encoding all potential thrombin receptor homologs related to SEQ ID NO:2, i.e., those thrombin receptor homologs having as little as 30% identity over at least 150 residues to SEQ ID NO:2.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of June 6, 1995. Much has happened in the development of recombinant DNA technology in the 17 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants and fragments at the time of filing of this application.

4. Summary

The Examiner failed to base the written description inquiry "on whatever is now claimed." Consequently, the Examiner did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In

addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Examiner.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed subject matter, and this rejection should be overturned.

Issue 5 – Whether claims 4, 5, and 57 are unpatentable over claims 1 and 3 of U.S. Patent No. 5,686,597

Claims 4, 5, and 57 stand rejected under 35 U.S.C. § 101 based on the allegation that they claim the same invention as that of claims 1 and 3 of prior U.S. Patent No. 5,686,597 (the '597 patent). This rejection is traversed.

Claims 4, 5, and 57 recite "isolated" polynucleotides while claims 1 and 3 of the '597 patent recite "isolated and **purified**" polynucleotides. An isolated polynucleotide comprising SEQ ID NO:1, or encoding a polypeptide comprising SEQ ID NO:2, can be produced **without purification** by, for example, chemical synthesis (Specification, e.g., at page 10, lines 15-19). Also, a composition comprising an isolated polynucleotide may have impurities. For example, a polynucleotide may be "isolated" from whole cells, but that polynucleotide isolate may have impurities.

This rejection is based on the Examiner's assertion that " 'isolated' means the same as 'purified', and 'isolated and purified' is merely redundant" (Office Action, February 12, 2003; page 8, § 7). However, the Examiner also asserts that "[p]urified is a relative term, and means 'removed from its natural source' " (*Id*). This latter assertion demonstrates that the Examiner is interpreting the limitation "purified" to mean that the claimed polynucleotides originate from a **natural source**. There is no requirement that the claimed isolated polynucleotides originate from a natural source. Even if the sequence of a polynucleotide is naturally occurring, the isolated polynucleotide can be produced outside of nature. For example, a polynucleotide can be chemically synthesized (Specification, e.g., at page 10, lines 15-19), even if it has the sequence of a naturally occurring polynucleotide.

One of skill in the art would reasonably understand that the term "purified" would encompass the separation of a pre-existing object from other materials (e.g., removal of an object from its natural source). In contrast, the term "isolated" could additionally encompass the production of an object in an environment separate from other materials. Therefore, the terms "purified" and "isolated" are not exactly the same, and the scope of the claims at issue differ from the scope of claims 1 and 3 of prior U.S. Patent No. 5,686,597.

For at least the above reasons, reversal of this rejection is requested.

Issue 6 – Whether claims 3, 4, 5, 12, 13, and 57 are unpatentable over claim 1 of U.S. Patent No. 5,869,633

Claims 3, 4, 5, 12, 13, and 57 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,869,633 (the '633 patent).

Appellants request that the requirement for submission of a Terminal Disclaimer with respect to the '633 patent be held in abeyance until such time that there is an indication of allowable subject matter. The Examiner has acknowledged that this rejection will be withdrawn upon filing of such a Terminal Disclaimer (Office Action, February 12, 2003; page 8, § 8A).

Issue 7 – Whether claims 3, 4, 5, 12, 13, and 57 are unpatentable over claims 1 and 3 of U.S. Patent No. 5,686,597

Claims 3, 4, 5, 12, 13, and 57 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 5,686,597 (the '597 patent).

Appellants request that the requirement for submission of a Terminal Disclaimer with respect to the '597 patent be held in abeyance until such time that there is an indication of allowable subject matter. The Examiner has acknowledged that this rejection will be withdrawn upon filing of such a Terminal Disclaimer (Office Action, February 12, 2003; page 8, § 8B).

Issue 8 – Whether claim 6 is unpatentable over claim 2 of U.S. Patent No. 5,686,597

Claim 6 stands rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 5,686,597 (the '597 patent).

Appellants request that the requirement for submission of a Terminal Disclaimer with respect to the '597 patent be held in abeyance until such time that there is an indication of allowable subject matter. The Examiner has acknowledged that this rejection will be withdrawn upon filing of such a Terminal Disclaimer (Office Action, February 12, 2003; page 8, § 8C).

Issue 9 – Whether claims 9 and 10 are unpatentable over claim 6 of U.S. Patent No. 5,686,597

Claims 9 and 10 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of U.S. Patent No. 5,686,597 (the '597 patent).

Appellants request that the requirement for submission of a Terminal Disclaimer with respect to the '597 patent be held in abeyance until such time that there is an indication of allowable subject matter. The Examiner has acknowledged that this rejection will be withdrawn upon filing of such a Terminal Disclaimer (Office Action, February 12, 2003; page 8, § 8D).

Issue 10 – Whether claims 6 and 7 are unpatentable over claims 4 and 5 of U.S. Patent No. 5,686,597

Claims 6 and 7 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4 and 5 of U.S. Patent No. 5,686,597 (the '597 patent).

Appellants request that the requirement for submission of a Terminal Disclaimer with respect to the '597 patent be held in abeyance until such time that there is an indication of allowable subject matter. The Examiner has acknowledged that this rejection will be withdrawn upon filing of such a Terminal Disclaimer (Office Action, February 12, 2003; page 8, § 8E).

(9) CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth by the Examiner and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

The enablement rejections, the written description rejections, and the statutory double patenting rejections should also be reversed, based on at least the arguments presented above.

Due to the urgency of this matter, and its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

This brief is enclosed in triplicate.

Respectfully submitted,

INCYTE CORPORATION

Date: June 25, 2003

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APPENDIX

Claims on appeal:

3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:2,

b) a polypeptide comprising a naturally occurring amino acid sequence, wherein the naturally occurring amino acid sequence differs from the amino acid sequence of SEQ ID NO:2 by a substitution of one amino acid residue and/or an insertion of 1-5 amino acid residues and/or a deletion of 1-5 amino acid residues,

c) a thrombin-binding fragment of a polypeptide, wherein the polypeptide has the amino acid sequence of SEQ ID NO:2, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:2, wherein said fragment comprises at least 13 contiguous amino acid residues of SEQ ID NO:2.

4. An isolated polynucleotide of claim 3 encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2.

5. The isolated polynucleotide of claim 4, comprising the polynucleotide sequence of SEQ ID NO:1.

6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.

7. A cell transformed with a recombinant polynucleotide of claim 6.

9. A method of producing a polypeptide encoded by a polynucleotide of claim 3, the method comprising:

a) culturing a cell under conditions wherein the polypeptide is expressed, and wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide of claim 3, and

b) recovering the polypeptide so expressed.

10. A method of claim 9, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO:2.

12. An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:1,

b) a polynucleotide comprising a naturally occurring human variant of the polynucleotide sequence of SEQ ID NO:1,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

13. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide selected from the group consisting of:

a) a polynucleotide consisting of the polynucleotide sequence of SEQ ID NO:1,

b) a polynucleotide consisting of a naturally occurring human variant of the polynucleotide sequence of SEQ ID NO:1,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

57. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:1.

58. An isolated polynucleotide of claim 12, comprising a naturally occurring human variant of the polynucleotide sequence of SEQ ID NO:1.